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EXAMINER	
ROYDS, LESLIE A	
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1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,037	SCHERER, WARREN J.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *3,4,7-10,14-17,19-25 and 27-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,11-13,18 and 26* is/are rejected.

7)☒ Claim(s) *18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/20/04;1[illegible]/05;1/22/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-33 are presented for examination.

Applicant's Information Disclosure Statements (IDS) filed April 20, 2004 (two pages), January 24, 2005 (one page) and January 22, 2007 (one page) have each been received and entered into the present application. As reflected by the attached, completed copies of form PTO/SB/08A-B (four pages total), the Examiner has considered the cited references.

Applicant's response filed March 12, 2007 to the requirement for restriction/election dated September 11, 2006 has been received and entered into the present application. Pursuant to the notice dated May 16, 2007, the response was held to be non-compliant for the reasons explained therein. Applicant's subsequent response filed June 4, 2007 to correct the non-compliance of the previous response has also been received and entered into the present application.

Requirement for Restriction/Election

Applicant's election **without traverse** of the invention of Group II (claims 5-6), directed to a method for treating cutaneous flushing as it results from menopause-associated hot flashes comprising the administration of an alpha-2-adrenergic receptor agonist, and election of species of brimonidine tartrate as the alpha-2-adrenergic receptor agonist for examination, in addition to the species of steroidal anti-inflammatory agents (i.e., hydrocortisone) as the additional agent for use in combination with the adrenergic agonist, for prosecution on the merits, in the replies filed March 12, 2007 and June 4, 2007, is acknowledged by the Examiner.

Upon reconsideration of the claims, the election of species of a single steroidal anti-inflammatory agent for examination on the merits is hereby **withdrawn**.

Claims 1-2, 11-21 and 26-28 have been identified as linking claims and will be examined herein with the elected invention insofar as they read upon the elected invention and species under examination.

Therefore, for the reasons above and those made of record at pages 2-9 of the previous Office Action dated September 11, 2006, the election requirement is deemed proper and is made **FINAL**.

Claims 3-4, 7-10, 14-17, 19-25 and 27-33 are **withdrawn** from further consideration pursuant to 37 C.F.R. 1.142(b), as being drawn to non-elected inventions.

The claims corresponding to the elected subject matter are claims 1-2, 5-6, 11-13, 18 and 26, and such claims are herein acted on the merits.

Expansion of Election of Species Requirement

A reasonable and comprehensive search conducted by the Examiner determined that the prior art at the time of the present invention was such that it did not anticipate, suggest or render obvious the concomitant use of, specifically, a steroidal anti-inflammatory agent in combination with the elected specie of alpha-2-adrenergic receptor agonist, brimonidine tartrate, for the treatment of cutaneous facial flushing caused by menopausal hot flashes. In light of this discovery, the search was expanded to cover the additional administration of an antioxidant compound for the treatment of the same.

Objection to the Claims

Claim 18 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 12, since they both encompass identical embodiments of the claimed invention. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. Please reference MPEP § 706.03(k).

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 5-6, 11-13, 18 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment, reduction or inhibition of cutaneous facial flushing caused by menopause-associated hot flashes by administering an effective amount of the selective alpha-2-adrenergic agonist brimonidine tartrate, does not reasonably provide enablement for the prevention of the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The present invention is directed to a method for treating cutaneous flushing in a human caused by abnormal, endogenously-induced vasomotor instability, such as, e.g., facial flushing caused by menopause-associated hot flashes, comprising administering to said human via topical dermatological application a composition comprising the selective alpha-2-adrenergic receptor agonist brimonidine

tartrate, admixed with a dermatologically acceptable carrier, in an amount effective to reduce, inhibit, reverse or prevent cutaneous facial flushing. The adrenergic agonist may be administered concomitantly with an additional agent, such as, e.g., a steroidal anti-inflammatory agent and/or an antioxidant compound (see, e.g., claim 12).

In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that an amount of the claimed selective alpha-2-adrenergic compound (i.e., brimonidine tartrate) could be administered for the prevention of cutaneous flushing caused by menopause-associated hot flashes without undue experimentation because the state of the art at the time of the invention did not recognize such an objective as generally possible to achieve.

As set forth in *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains the teachings of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112, *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support;* assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added)

The present claims circumscribe the use and administration of the presently claimed selective alpha-2-adrenergic agonist, i.e., brimonidine tartrate, for the prevention of cutaneous facial flushing caused by menopausal hot flashes. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that, by administering a therapeutically effective amount of the claimed adrenergic agonist, menopausal hot flashes and, thus, the cutaneous facial flushing resulting from

the same, would actually be prevented from developing. In other words, the skilled artisan would have understood the term "prevent", in its broadest reasonable interpretation consistent with MPEP §2111, to mean that the incidence of facial flushing from menopausal hot flashes after administration of the selective alpha-2-adrenergic agonist brimonidine tartrate would essentially be 0% and could be reasonably expected not to develop, occur, recur or worsen. In light of the fact that the specification fails to provide the skilled artisan with any direction or guidance as to how such objectives could actually be achieved, since the disclosure is solely directed to the concept of treating patients that already exhibit (or are exhibiting) cutaneous facial flushing associated with menopausal hot flashes and are diagnosed with the same, the present specification is viewed as lacking an enabling disclosure of the entire scope of the claimed invention.

Regarding the prevention of cutaneous facial flushing caused by menopausal hot flashes, the objective truth that such flushing could be prevented from occurring is doubted because the state of the art with regard to the definitive prevention of menopausal hot flashes (and, thus, the cutaneous flushing associated therewith) is underdeveloped due to the complexity and the lack of pathophysiological understanding of the condition.

The objective truth of the statement that cutaneous flushing caused by menopausal hot flashes may be prevented from occurring is doubted because the understanding of the etiology, mechanism of action and factors that trigger hot flashes is not particularly well developed. This is acknowledged by Bachmann, who teaches, "The cause of the hot flush remains speculative, but it is thought to be due to a combination of hormonal, metabolic, and psychogenic factors. Hot flushes are associated with vasodilation and skin temperature increases that result in sweating, decreased skin resistance, and improved skin conductance. Data from a study by Mashchak et al. indicated that vasomotor flushes result from a sudden change in hypothalamic control of temperature regulation. Later investigations suggested that estrogen withdrawal is the precipitating factor for hot flushes in menopausal women. For example,

Silva et al. demonstrated that estrogen can modulate the firing rate of thermosensitive neurons in the preoptic area of the hypothalamus in response to thermal stimulation in the rat. Other physiologically based studies indicate that the responsiveness of arterioles to catecholamines is greater in women with hot flushes than in those without hot flushes. Estrogen appears to enhance alpha-2-adrenergic activity, and estrogen withdrawal may therefore lead to vasomotor flushes as a result of reduced alpha-2-adrenergic activity." (p.S312, col.1-2, "Etiology")

This complex nature and poor understanding of menopausal hot flashes is corroborated by both Stearns et al. ("Cooling Off Hot Flashes", *Journal of Clinical Oncology*, 20(6); 2002:1436-1438) and Miller et al. ("Measuring Hot Flashes: Summary of a National Institutes of Health Workshop", *Mayo Clinic Proceedings*, June 2004, 79(6):777-781). Stearns et al. teaches, "Although hot flashes are common, the pathophysiology of the phenomenon is not well understood. Estrogen action in the CNS is complex. Estrogen exerts its function not only through an interaction with its receptors but also through an interaction with other receptors important in regulation of sleep, mood, and cognition. During menopause, there is a decline in hormone levels and, as a result, there is an alteration in the CNS thermoregulatory set point. Then, after a trigger, immediate changes in hormones or neurotransmitters lead to the hot flash sensation. Several changes in hormone and neurotransmitter levels may proceed or coincide with the hot flash. However, a biochemical trigger for hot flashes has not been found." (col.1, para.2, p.1436)

Miller et al. is cited for its teaching that, "The etiology and mechanism of hot flashes remain incompletely understood. Future studies of hormonal and neurologic systems may provide promising leads to improve our understanding of the basic phenomenon and perhaps also shed light on the placebo effect. However, this is likely a complex undertaking. Critical to this effort is the ability to reliably identify when a hot flash has occurred...The factors that we want to measure with respect to hot flashes are likely to change over time as more is learned about the underlying phenomenon. This will probably

be an evolutionary process, one involving decisions about what biological factors will be most useful for the task at hand, what technologies might be available or easily adaptable, which measures should be bundled together to maximize the precision of data collected with the available technology, and the analysis of the data to generate new hypotheses and perhaps the need for new measurement tools...Investigators interested in studying hot flashes face complex issues. The incomplete understanding of the basic physiology underlying hot flashes clearly calls for further work in this area. Some mechanistic studies cannot be conducted with human subjects; thus, animal models are needed. Animal models could be particularly helpful for understanding the neurobiology of hot flashes and perhaps placebo effects." (p.779-780, "Summary")

Given the exceedingly poor understanding of both the etiology and mechanism of menopausal hot flashes, and in view of the number of biological triggers that have been proposed, but not confirmed, to be involved in the development of menopausal hot flashes, one of ordinary skill in the art would have been skeptical to accept, on its face, Applicant's statement that the cutaneous facial flushing resulting from menopausal hot flashes could be prevented using the presently claimed selective alpha-2-adrenergic agonist, brimonidine tartrate. In fact, such complexity of even diagnosing menopausal hot flashes, coupled with this clear lack of understanding of the pathophysiology of the condition, precludes a common, art-accepted protocol for preventing flushing caused by menopausal hot flashes in any female patient, given the subjectivity of diagnosis. Furthermore, the fact that the art only recognizes therapies that may have some efficacy in *treating* the condition, in view of the fact that no therapy has yet been identified that is capable of clearly preventing the condition, is clear evidence that the objective of prevention using an agent capable of agonizing but one of a multitude of biochemical triggers proposed to be involved in the development and onset of menopausal hot flashes would have been an outcome not reasonably expected by one of ordinary skill in the art at the time of the invention.

In other words, the condition is sufficiently complicated and poorly understood such that the idea

that any active agent (including that presently claimed) would be capable of preventing the onset of (or even curing) such a condition via administration of the presently claimed active agent would not have been reasonably expected by the skilled artisan. The artisan would have required sufficient direction as to how the population of patients in need of such prevention could be identified and how the presently claimed active agent could actually prevent flushing caused by menopausal hot flashes such that the artisan would have been imbued with at least a reasonable expectation of success. Such success would not have been reasonably expected given that the concept of a single agent, or even a combination of agents, that is effective against the development of flushing due to menopausal hot flashes would have been unique and, thus, met with a great deal of skepticism.

It is in this regard that Applicant is directed to the MPEP at §2164.08. All questions of enablement are evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involved the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to use the *entire scope* of the claimed invention without undue experimentation.

Applicant fails to provide even a single example of the claimed compound in treating, let alone preventing, cutaneous flushing caused by menopausal hot flashes. While a lack of a working embodiment cannot be the sole factor in determining enablement, the absence of substantial evidence commensurate in scope with the presently claimed subject matter, in light of the unpredictable nature of the art and the direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole. The instant specification conspicuously lacks any disclosure or teaching of manner and process of using the presently claimed compounds for

achieving the objective of preventing cutaneous flushing caused by menopausal hot flashes. Nowhere does the specification disclose the manner or procedure of using the presently claimed active agent for preventing the onset of the same such that the skilled artisan would have been imbued with at least a reasonable expectation of success in actually achieving such an objective without the burden of an undue level of experimentation.

The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the pharmaceutical and chemical arts that experimentation in this particular art is not at all uncommon, but that the level of experimentation required in order to practice this aspect of the invention in the absence of any enabling direction by Applicant would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added)

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that the objective of preventing cutaneous facial flushing caused by menopause-associated hot flashes by administering an effective amount of the selective alpha-2-adrenergic agonist brimonidine tartrate in a human could be achieved. In order to actually achieve such a result, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the presently claimed invention.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 5-6, 11-13, 18 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 1, and the claims dependent therefrom, is directed to a method for treating cutaneous flushing, i.e., facial flushing caused by menopause-associated hot flashes, caused by abnormal, endogenously-induced vasomotor instability comprising administering to said human via topical dermatological application, a composition comprising at least one selective alpha-2-adrenergic receptor agonist admixed with a dermatologically acceptable carrier, in an amount effective to reduce, inhibit, reverse or prevent cutaneous facial flushing. Present claim 26 is substantially identical to claim 1, but is directed to practice of the method in "an individual" rather than "a human".

In particular, it is noted that present claims 1-2, 5-6, 11-13, 18 and 26 read upon a method for treating cutaneous flushing in humans or in an individual, but Applicant has failed to connect the preamble objective of treating cutaneous flushing to the human or individual actually being treated by the method. For example, it is not clear whether the subject is actually suffering from cutaneous flushing caused by menopause-associated hot flashes or whether the method is intended for practice in any patient who may or may not have such a condition. In other words, Applicant has not made clear on the record whether the human is one in need of treatment of cutaneous flushing.

Furthermore, Applicant has also failed to clearly connect the therapeutic objective of the preamble, i.e., treating cutaneous flushing, with the effective amount to be administered. Specifically, the claimed objective is the treatment of cutaneous flushing, but the effective amount as claimed is intended to be effective "to reduce, inhibit, reverse or prevent cutaneous facial flushing." Accordingly, the claims

fail to clearly, precisely and deliberately set forth the intended therapeutic objective (i.e., cutaneous flushing *per se* or cutaneous facial flushing) and the intended effect of the amount of the active agent (i.e., treatment, reduction, inhibition, reversal or prevention) on the intended therapeutic objective.

For these reasons, the metes and bounds of the present claims cannot be identified and one of ordinary skill in the art would not necessarily be reasonably apprised of the scope of the claims. In light of such, claims 1-2, 5-6, 11-13, 18 and 26 fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 5-6, 11-13, 18 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wymenga et al. ("Management of Hot Flushes in Breast Cancer Patients", *Acta Oncologia*, 41(3), 2002; 269-275) in view of Gil et al. (U.S. Patent Application Publication No. 2003/0229088; Issued December 2003, Filed May 2002).

Wymenga et al. teaches treatment of menopausal symptoms, such as hot flushes, with alternative therapies other than hormone replacement therapy, which is contraindicated in patients suffering from breast cancer (abstract) due to the potential growth-promoting effects on residual tumor cells (col.2, para.2, p.269). Wymenga et al. further teaches that menopausal flushing onset is abrupt and typically starts with a feeling of heat in the upper body that is generally associated with a visible reddening of the face (col.1, para.4, p.270). Wymenga et al. discloses the use of clonidine, a centrally active alpha-adrenergic agonist that reduces vascular reactivity, in low dosages that was demonstrated to be effective

in the reduction of hot flushes caused by normal menopause either when administered orally or transdermally (col.2, para.4, p.271). Wymenga et al. further discloses that the administration of vitamin E (i.e., an antioxidant; see present claims 11-12 and 18) in an amount of 800 I.U. per day to patients experiencing hot flushes demonstrated a significant reduction in flushing, which, though on average was only a reduction in one flushing incident per day, was still suggested for use in treating hot flushes due to its non-toxic and inexpensive properties, as well as the fact that it is widely available (col.2, para.2, p.272).

The differences between the Wymenga et al. reference and the instantly claimed subject matter lies in that the reference fails to specifically teach the use of the alpha-2-adrenergic agonist, brimonidine tartrate, or the express combination of an antioxidant (i.e., vitamin E) in combination with the alpha-adrenergic agonist as presently claimed.

However, Gil et al. is cited for its teaching of known alpha-adrenergic agonists, including clonidine, brimonidine, tizanidine, etc. (p.1, para.[0009]) and salts thereof, including the tartrate salt (p.13, para.[0091]), and compositions thereof (p.13, para.[0096]) in dermatologically acceptable formulations, such as, e.g., a dermal patch, topical drops, creams gels or ointments, etc. (p.14, para.[0099]).

One of ordinary skill in the art would have found it *prima facie* obvious to use the brimonidine alpha-adrenergic agonist (or the tartrate salt thereof) as taught by Gil et al. for the treatment of menopausal hot flushes and the cutaneous flushing associated with the same because Gil et al. teaches such a compound as having potent activity in agonizing the alpha-adrenergic receptor and Wymenga et al. teaches significant reduction in the incidence of hot flushes in menopausal women when treated with an alpha-adrenergic agonist (i.e., clonidine) orally or transdermally. Such a person would have been motivated to do so because the brimonidine (or tartrate salt thereof) of Gil et al. was functionally equivalent for binding alpha-adrenergic receptor as the clonidine compound disclosed by Wymenga et al.

for use in reducing the incidence of hot flushing in menopausal women. Thus, substituting the clonidine of Wymenga et al. with the brimonidine compound of Gil et al. would have been *prima facie* obvious and well within the purview of the skilled artisan because the same end result of agonizing alpha-adrenergic receptors and thereby reducing menopausal hot flushes would have been achieved, absent factual evidence to the contrary. Furthermore, the fact that Gil et al. confirms the amenability of brimonidine into a dermatologically acceptable formulations raises the reasonable expectation of success that the skilled artisan would have substituted the brimonidine compound of Gil et al. for the transdermal administration of clonidine as taught by Wymenga et al. and would have likely achieved the same, or at least substantially similar, reduction in the incidence of menopausal hot flushes and the cutaneous flushing associated therewith.

The MPEP states at §2144.06, "In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents." Because the Examiner has shown that the functional equivalency of the compounds was known in the prior art at the time of the invention, the present finding of obviousness is proper and firmly grounded in the teachings of the MPEP at §2144.06.

Applicant's attention is further drawn to the MPEP at §2144.06, which states, "An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

Furthermore, one of skill in the art would have also found it *prima facie* obvious to combine the alpha-adrenergic agonist with the vitamin E compound in light of the disclosure of Wymenga et al. because Wymenga et al. teaches the activity of both the alpha-adrenergic agonist (i.e., clonidine) and vitamin E in effecting a significant reduction in the incidence of menopausal hot flushes and, thus, the cutaneous flushing associated therewith. Motivation to administer both compounds together flows

logically from the very fact that each discrete agent was known in the prior art to have the same therapeutic utility and, in turn, raises the reasonable expectation of success that the two agents, when combined, would have, at minimum, additive, if not synergistic, effects in reducing the incidence of menopausal hot flushes (and the cutaneous flushing that results from the same) when combined.

As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980): "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960)."

Conclusion

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Please reference the publication to Waldinger et al. ("Treatment of Hot Flushes with Mirtazapine: Four Case Reports", *Maturitas*, 36; 2000:165-168).

Rejection of claims 1-2, 5-6, 11-13, 18 and 26 is proper.

Claims 3-4, 7-10, 14-17, 19-25 and 27-33 are **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leslie A. Royds
Patent Examiner
Art Unit 1614

August 15, 2007